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Meli, Madeleine ; Gitzelmann, Gabriela ; Koppensteiner, Renate ; Amann-Vesti, Beatrice R

Abstract: The objective of this study was to evaluate the long-term follow-up of patients with Raynaud's phenomenon (RP) and pathological nailfold capillaroscopy (NC) in order to analyse the predictive value of specific features of capillaroscopy for the development of a connective tissue disease (CTD). From 1992 to 2002, NC alone or combined with fluorescence videomicroscopy with sodium fluorescein (NaF) was performed in 1024 consecutive patients because of RP. We analysed the follow-up and pathological features of NC in all patients who had neither clinical nor serological signs of a CTD at the time of NC. Of 308 patients with neither serological findings nor clinical signs of CTD but with RP and pathological features in NC suspicious for CTD, follow-up data were available for 133 patients. An additional NaF test had been performed in 51 (38.4%) patients. After a mean follow-up of 6.5 years (range: 1-15 years), 109 patients had developed a CTD and 24 patients did not show any clinical signs or serological markers for a CTD after a mean follow-up of 8.5 years (range: 2-15 years). There were no differences in age, duration of RP or of follow-up in patients who developed a CTD compared to patients who did not. Significantly more giant capillaries (p=0.0001), avascular fields (p=0.02) and irregular architecture (p=0.0001) had been observed in patients who had developed a CTD during the follow-up of 6.5 years. The presence of giant capillaries, avascular fields and irregular architecture of nailfold capillaries is predictive for the development of a CTD in patients with RP

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ORIGINAL ARTICLE

Madeleine Meli · Gabriela Gitzelmann
Renate Koppensteiner · Beatrice R. Amann-Vesti

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Abstract The objective of this study was to evaluate the long-term follow-up of patients with Raynaud's phenomenon (RP) and pathological nailfold capillaroscopy (NC) in order to analyse the predictive value of specific features of capillaroscopy for the development of a connective tissue disease (CTD). From 1992 to 2002, NC alone or combined with fluorescence videomicroscopy with sodium fluorescein (NaF) was performed in 1024 consecutive patients because of RP. We analysed the follow-up and pathological features of NC in all patients who had neither clinical nor serological signs of a CTD at the time of NC. Of 308 patients with neither serological findings nor clinical signs of CTD but with RP and pathological features in NC suspicious for CTD, follow-up data were available for 133 patients. An additional NaF test had been performed in 51 (38.4%) patients. After a mean follow-up of 6.5 years (range: 1–15 years), 109 patients had developed a CTD and 24 patients did not show any clinical signs or serological markers for a CTD after a mean follow-up of 8.5 years (range: 2–15 years). There were no differences in age, duration of RP or of follow-up in patients who developed a CTD compared to patients who did not. Significantly more giant capillaries ($p=0.0001$), avascular fields ($p=0.02$) and irregular architecture ($p=0.0001$) had been observed in patients who had developed a CTD during the follow-up of 6.5 years. The presence of giant capillaries, avascular fields and irregular architecture of nailfold capillaries is predictive for the development of a CTD in patients with RP.

M. Meli · G. Gitzelmann
R. Koppensteiner · B. R. Amann-Vesti (✉)
Division of Angiology, Department of Internal Medicine,
University Hospital, Ramistrasse 100,
8091 Zurich, Switzerland
E-mail: beatrice.amann@usz.ch
Tel.: +41-1-2551111
Fax: +41-1-2554510

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Introduction

Raynaud's phenomenon (RP) is classified as primary when no underlying cause can be identified and as secondary when its presence is explained by an associated condition such as systemic lupus erythematosus (SLE) and systemic sclerosis. Estimates of the prevalence of RP in the general population range from 5 to 20% [1], and 3–5% have been reported to develop a connective tissue disease (CTD) within 3–6 years [2]. In scleroderma, RP has been reported to be the presenting sign in 50–70% of patients and in 15% of patients with SLE [3–5]. However, RP may precede the development of the disease by many years. In several small studies it has been reported that the presence of autoantibodies may predict the presence or future development of systemic disease [6–8].

Nailfold capillaroscopy (NC) allows the in vivo assessment of morphology and of some functional aspects of cutaneous capillaries and has been accepted as a diagnostic tool for evaluating microvascular involvement in systemic sclerosis, dermatomyositis, overlap syndromes and SLE [9–12]. Only little is known about the role of NC in identifying patients with RP who are at risk of developing a CTD [13–15]. Furthermore, by fluorescence videomicroscopy with sodium fluorescein (NaF) patients with a CTD might exhibit halo enlargement with a typical "dwarf hat" formation as a sign of disturbed barrier function of the vessel wall and structural changes of the pericapillary space [16]. However, it has been shown in one study that of 69 patients with CTD 16% had normal findings in conventional NC but pathological halo formation after NaF injection [17]. The predictive value of combined NC with NaF has not been studied yet. In the present report, we describe the follow-up of 133 patients with pathological findings in NC with

or without NaF who were referred to our clinic because of RP. At the time of the study, all patients had negative autoantibodies and no other clinical signs of a CTD.

Patients and methods

In the period from 1992 to 2002, 1024 patients were referred to our institution for vascular assessment including NC because of a history of RP of the hands and fingers. In all patients NC was performed; fluorescence videomicroscopy with NaF was only performed in part of the patients. Exclusion criteria for NaF were drug or food allergies, history of renal disease, pathological creatinine clearance, and pregnancy. In some cases the NaF test was not performed because of difficulties in puncturing a vein or no specific reason was given. Fluorescence videomicroscopy with NaF was performed as previously described [18]. NC was performed with a fluorescence videomicroscopy system consisting of an incident light fluorescence microscope (Leica, Heerbrugg, Switzerland), a 3-CCD video camera (model DXC-930P, Sony, Tokyo, Japan) with a camera adapter and sensitivity set on automatic control (CMA-D2, Sony), a video timer (VTG-22) and scale marker (IV-600, both from For-A-Company, Tokyo, Japan), a video monitor (Picture Monitor model PM 171T, Ikegami Tsushinki, Tokyo, Japan) and a video tape recorder (S-VHS, AG-7350, Panasonic, Osaka, Japan). The microscope is equipped with 1.0/0.04, 2.5/0.08, 6.3/0.20 and 10/0.25 planar objectives (Leica, Heerbrugg, Switzerland), which allow a magnification of 24, 62, 165 and 240 times, respectively, on the monitor. The fluorescence excitation filter works at 450–490 nm and the barrier filter at 515 nm. The NaF was injected into the antecubital vein as a bolus; the dosage was adjusted according to the estimated blood volume. At our institution 0.2–0.3 ml NaF 20% per liter estimated blood volume is used and is adequate for visualization of skin capillaries.

The following parameters of NC were evaluated from the videotape [19]:

- Irregular architecture (capillaries not in one row as normal, small areas (< 500 μm) with missing capillaries next to areas with clusters of capillaries)
- Avascular fields (loss of capillaries in a field of at least 500 μm)
- Dilatation of capillaries (arterial side > 15 μm, venous side > 20 μm)
- Giant capillaries (apical diameter > 50 μm, Fig. 1)
- NaF images were evaluated for apical halo enlargement or "dwarf hat" formation, respectively (Fig. 2) [16].

Diagnostic criteria

The diagnosis of systemic sclerosis (Scl) was made according to the preliminary criteria of the American Rheumatism Association (ARA) [20]. The diagnosis of CREST was made when the following criteria were fulfilled: calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia in the

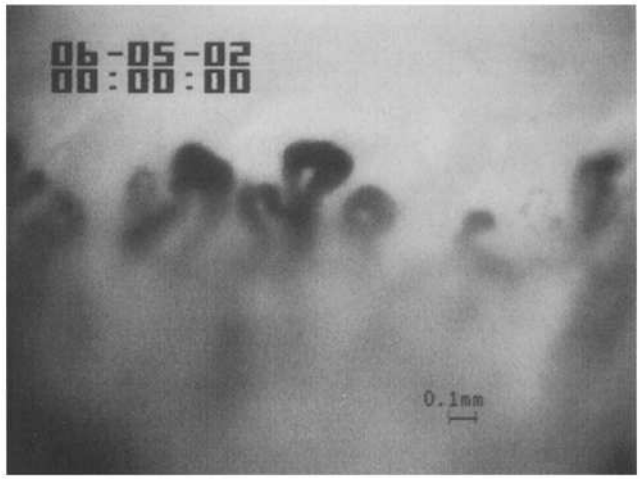

Fig. 1 Typical giant capillary of the nailfold in a female patient with RP who developed CREST 10 years after NC (×63).

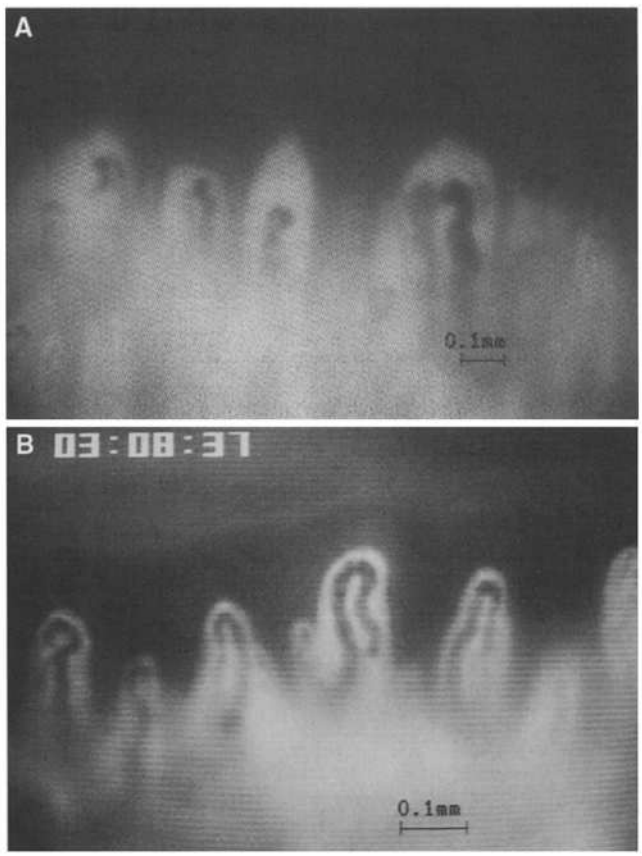

Fig. 2 a After the intravenous injection of NaF apical halo enlargement or "dwarf hat" formation might be seen in patients with CTD. **b** In healthy subjects the cells are surrounded by the fluorescent plasma layer and NaF does not pass the narrow pericapillary border (×63).

presence of anticentromere antibodies. Mixed connective tissue disease (MCTD) was diagnosed in the presence of symptoms as described by Alarcon-Segovia and Cardiel [21]. The diagnoses of SLE and rheumatoid arthritis (RA) were based on the diagnostic criteria of the ARA. Dermatomyositis (DM) was considered the diagnosis when the criteria of Bohan and Peter [22] were present. Sjögren's syndrome was diagnosed when the diagnostic criteria from the American–European Consensus Group were present, including the presence of autoantibodies (anti-Ro/SSA, anti-La/SSB or both) [23].

Statistical analysis

Analyses were performed with the statistical software package Stat View 5.0. Continuous variables are reported as means and categorical variables as percentages. Comparison between groups of patients was done by means of unpaired Student's *t*-test and for categorical variables by using Fisher's exact test. A test for logistic regression was performed as a means of studying the diagnostic value of the different features of NC to predict development of CTD. Significance was defined as $p < 0.05$.

Results

Of a total of 1024 patients seen with RP between 1992 and 2002, the results of 968 patients were evaluated for the present study; 19 patients with Osler's disease and 37 patients for whom some data were missing had been excluded. In 693 patients, the NaF test was performed in addition to conventional NC. In 201 (155 females and 46 males) patients referred to us because of RP the diagnosis of a CTD had already been made at the time of NC due to serological features and the above-mentioned criteria. The diagnosis and results of NC from these 201 patients are shown in Table 1. Microangiopathy was defined as being present if at least one of the above-mentioned criteria was found. The diagnosis of primary RP was made in 459 patients because the following criteria were fulfilled: normal findings in NC, negative autoantibodies, no signs of a CTD according to the ARA criteria, no calcinosis, no oesophageal motility disturbances, no sclerodactyly, no telangiectasia and no xerostomia. In 308 patients with normal serological findings and no clinical signs of a CTD despite RP, we found pathological features in NC suspicious for CTD. Of these 308 patients with RP and microangiopathy in NC, follow-up data were available for 133 patients: 107 females (mean age: 50.0 years, range: 10–89 years) and 26 males (mean age: 55.1 years, range: 26–82 years). The NaF had been administered in 51 (38.4%) patients. After a mean follow-up of 6.5 years (range: 1–15 years), 109 patients (82%, group 1) had developed a CTD according to the above-described criteria. The patient characteristics, diagnoses and findings of NC in these patients are shown in Table 2.

The remaining 24 patients (group 2, 19 females, 5 males, mean age: 45.6 years, range: 21–70) had not developed any clinical signs of a CTD and serological tests were still negative after a mean follow-up of 8.5 years (range: 2–15 years). Patient characteristics and features of NC are shown in Table 3. There were no statistically significant differences in age, duration of RP or duration of follow-up in patients who developed a CTD (group 1) compared to patients who had not developed a CTD (group 2) during the follow-up. For comparison between the two groups, only patients who had not developed a CTD after a follow-up of at least 6 years had been included: four patients with a follow-up of 4 years (two patients), one patient with a follow-up of 5 years and one patient with a follow-up of 2 years had been excluded from the analysis [2]. The mean follow-up of these 20 patients was 9.3 years (range: 6–15 years). The features and comparison of NC in the two groups are shown in Fig. 3. In group 1 significantly more giant capillaries ($p = 0.0001$), avascular fields ($p = 0.02$) and irregular architecture ($p = 0.0001$) had been observed at the initial investigation. Including all 24 patients the results were almost identical; the same features (giant capillaries, avascular fields and irregular architecture) had been identified as significantly different in the two groups ($p < 0.05$).

Furthermore, the presence of giant capillaries or an irregular architecture was predictive for the development of a CTD ($p < 0.005$). Only two patients developed SLE

Table 1 Age, sex and presence or absence of pathological features in nailfold capillaroscopy (NC) of 201 patients with RP, in whom an underlying disease had been already diagnosed at the time of NC. *Scl* systemic sclerosis, *CREST* calcinosis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly, telangiecstasia, *SLE* systemic lupus erythematosus, *MCTD* mixed connective tissue disease, *DM* dermatomyositis, *RA* rheumatoid arthritis

Diagnosis	Patients (*n*/%)	Age (mean, range, years)	Female/male (%)	Presence of microangiopathy (%)	
				Yes	No
Scl	93/46.3	52.4 (13–78)	72.0/28.0	83.9	16.1
CREST	8/4.0	62.4 (36–76)	87.5/12.5	87.5	12.5
SLE	29/14.4	39.1 (12–63)	82.8/17.2	37.9	62.1
MCTD	29/14.4	50.7 (27–83)	86.2/13.8	65.5	34.5
DM	14/7.0	52.6 (17–70)	57.1/42.9	57.1	42.9
Sjögren's syndrome	9/4.5	52.6 (17–69)	88.9/11.1	44.5	55.5
RA	19/9.4	50.3 (22–73)	84.2/15.8	31.6	68.4
Total	201	51.5 (12–83)	77.1/22.9	60.7	39.3

Table 2 Characteristics of 109 patients with RP and pathological features in the nailfold capillaroscopy and their diagnosis after a mean follow-up of 6.5 years (1–15 years). *Scl* systemic sclerosis, *CREST* calcinosis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly, telangiecstasia, *SLE* systemic lupus erythematosus, *MCTD* mixed connective tissue disease, *DM* dermatomyositis

Diagnosis	Patients (*n*)	Age (years)	Female/male	Duration of RP (years)	Giant capillaries (%)	Dilated capillaries (%)	Avascular fields (%)	Irregular (%)	NaF performed (%)/halo (%)
Scl	46	51.1 (16–75)	80.4/19.6	5.1 (0.5–45)	89.1	89.1	19.5	73.9	28.3/77.0
CREST	30	57.1 (10–89)	83.3/16.7	8.4 (0.5–49)	80.0	90.0	30.0	60.0	30.0/89.0
SLE	2	57.0 (55–59)	100/0	7.0 (1–13)	100	100	50.0	100	100/100
MCTD	29	52.5 (10–82)	75.9 /24.1	8.5 (0.5–40)	62.1	90.0	20.7	58.6	48.3/85.7
DM	2	65.5 (59–72)	100/0	0.5	100	100	50.0	100	100/100
Total	109	52.9 (10–89)	88/21	6.9 (0.5–49)	79.8	89.9	23.8	67.0	34.0/81.6

Table 3 Characteristics of 24 patients with RP and pathological features in the nailfold capillaroscopy who did not develop CTD after a mean follow-up of 8.5 years (2–15 years)

Patients (*n*)	Age (years)	Female/male (%)	Duration of RP (years)	Giant capillaries (%)	Dilated capillaries (%)	Avascular fields (%)	Irregular (%)	NaF performed (%)/halo (%)
24	45.6 (21–70)	79.2/20.8	6.5 (1–20)	41.7	83.3	4.1	29.2	58.3/85.7

and DM, respectively; therefore no conclusions for these diseases can be drawn from our data.

Discussion

NC has been accepted as one of the most valuable diagnostic tools for the early detection of CTD, in particular for Scl and CREST [24–26]. In the present study, we analysed the features of NC in patients with RP in order to evaluate the predictive value of pathological findings. We found that during the mean follow-up of 6.5 years 82% of patients with RP and pathological findings in NC developed a CTD, mainly Scl, CREST and MCTD. These patients had shown significantly more giant capillaries, irregular architecture and avascular fields in the initial NC than the group who did not develop a CTD. The presence of giant capillaries and irregular architecture in NC were both predictive for the development of a CTD in our patient population.

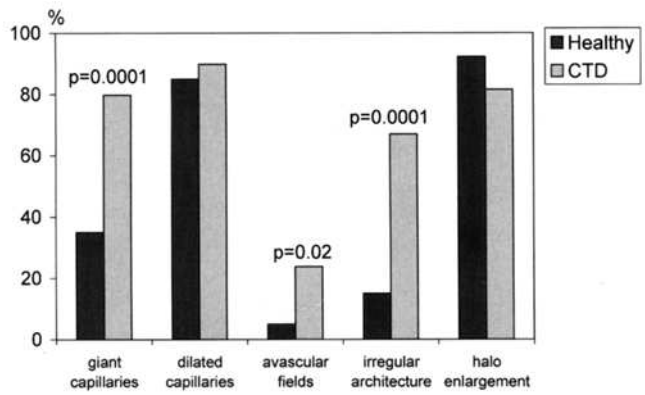

Fig. 3 Comparison of features of nailfold capillaroscopy in patients with RP. In patients who developed a connective tissue disease (*CTD*) during follow-up significantly more giant capillaries ($p=0.0001$), avascular fields ($p=0.02$) and irregular architecture ($p=0.0001$) have been found than in the 20 patients without any laboratory or clinical signs of a CTD after a follow-up of at least 6 years (mean follow-up: 9.3 years, range: 6–15 years). The enlargement of the apical halo after injection of NaF was not different in the two groups.

It has been shown that patients with CTD, especially with Scl and CREST, a typical "cap" formation or "lake-like" areas can be seen at the apex of the capillary after injection of NaF as a sign of disturbed barriers for diffusion of the dye at the capillary wall and at the outer border of the skin papilla (halo) [17, 27]. In 38.4% of our patients with RP, the NaF test was performed. We found a pathological apical diffusion in 81.6% of patients who developed a CTD during the follow-up; however, 85.7% of patients without any signs of a CTD after a mean follow-up of 8.5 years also showed the same halo pattern. From our data we can conclude that the additional use of NaF does not facilitate early detection of a CTD. However, even when we analyse only patients with a follow-up of at least 6 years the presence of pathological halo formation was not predictive for CTD.

Dilated capillaries were a very common but unspecific finding in our patient population. They were present in over 80% and their presence was not predictive for the development of a CTD. However, they have been described in CTD, in acrocyanosis and less pronounced in primary RP [28, 29]. In CTD dilated capillaries are usually not the only pathological feature of NC, whereas in primary RP and primary acrocyanosis additional pathological features such as giant capillaries or avascular fields are missing.

It is known that a CTD might develop many years after the onset of RP; therefore, the Allen and Brown criteria requiring at least a 2-year history of RP for the diagnosis of a primary RP have been revised [30]. In our analysis the mean duration of RP at the time of NC was 6.9 years in the group who developed a CTD and 6.5 years in the group who did not. In patients who developed a CTD during the follow-up, duration of RP up to 49 years has been reported. Our data suggest that the duration of RP is a very poor criterion for identifying patients at risk for the development of secondary RP.

The mean age was not different in the two patient groups, although children and very young adults (age between 10 and 21) were only seen in the group who developed a CTD during the follow-up. The number might be too low for a conclusion, but it suggests that in children and young adults with RP and pathological capillaries the risk for an underlying disease is higher.

In 201 patients (77.1% female) the diagnosis of an underlying disease had already been made at the time of NC. About half of the patients had been diagnosed with a form of Scl; in these patients a microangiopathy in NC was present in over 80%. In contrast, only in 37.9% of patients with SLE was microangiopathy present. Pathological capillary morphology has been reported in 2–90% of SLE patients [10, 31]. This variation in published numbers might be due, at least in part, to the definition of microangiopathy used by the authors. Furthermore, it has been speculated that the presence of microangiopathy might be associated with clinical features, such as RP or specific antibodies. Furtado et al. [32] found a significant association between microangiopathy in SLE and RP, and similar findings were reported by Caspary et al. [33]; however, in a study of 51 patients with SLE Bongard et al. [34] found no correlation between abnormal capillaroscopic findings and RP. In our study, only patients with RP were included, which might be one reason for the rather high incidence of microangiopathy in our group. A higher incidence of microangiopathy among SLE patients with positive anticardiolipin and anti-U1 ribonucleoprotein antibodies has been demonstrated, suggesting direct damage to the endothelium by these antibodies [32, 34]. However, specific autoantibodies in Scl patients (i.e. anti-Scl-70 and anticardiolipin antibody) do not seem directly linked to the expression of a singular capillaroscopic pattern [35].

In conclusion, in patients presenting with RP the presence of either giant capillaries, avascular fields or irregular architecture in NC is predictive for the development of a CTD, mainly scleroderma, CREST and MCTD. NC may not be a valuable diagnostic tool in SLE, but it might be helpful in identifying a subgroup of patients with different evolution and prognosis of the disease. The duration of RP was not a criterion for the risk of future development of CTD. Despite the fact that in Scl a specific diffusion pattern after NaF injection might be present, the additional use of NaF does not facilitate early detection of a CTD.

Take home message

In patients with RP and negative serological tests, the presence of giant capillaries, avascular fields or irregular architecture in NC is predictive for the development of a CTD, mainly scleroderma, CREST and MCTD. Based on our data the duration of RP is not a criterion for the risk of future development of CTD.

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